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(54) Title: PHARMACEUTICAL POWDER COMPOSITION CONTAINING NON-IONIC CELLULOSE ETHER DERIVATIVE AND A CHITIN-DERIVED POLYMER

(57) Abstract

A pharmaceutical composition in powder form comprising a drug and a pharmaceutically-acceptable carrier, the carrier comprising a non-ionic cellulose ether derivative and a chitin-derived polymer. The pharmaceutical composition provides a high availability of the active ingredient and displays improved adhesion characteristics.

*uniform distribution*

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PHARMACEUTICAL POWDER COMPOSITION CONTAINING NON-IONIC  
CELLULOSE ETHER DERIVATIVE AND A CHITIN-DERIVED POLYMER

This invention relates to a pharmaceutical composition in powder form for application to the nasal mucosa. In particular, it relates to a sustained-release pharmaceutical composition in powder form comprising a drug, a nonionic cellulose ether derivative and a chitin-derived polymer which provides a high availability of the active ingredient, improved adhesion to the nasal mucosa, solves the common problem of "roll-back" commonly associated with spray and drop formulations such as decongestants and prevents the nasty aftertaste of the formulation active ingredient.

Background of the Invention

Various pharmaceutical preparations for application to the nasal cavity such as nasal ointments, jellies, nose drops and sprays are known in the art. Nasal ointments and jellies are unsatisfactory, however, because it is difficult to apply them to deep parts of the nasal cavity, such as the concha nasalis superior. Nose drops and sprays have the disadvantage, moreover, that it is difficult to retain the active drugs contained therein in the nasal cavity for an extended period of time. In addition, they are not efficient sustained-release formulations.

In the prior art, attempts have been made to prepare sustained-release formulations for application to the nasal mucosa. US-A-4,226,848 discloses a sustained-release pharmaceutical composition for application to the nasal

**SUBSTITUTE SHEET**

mucosa containing a drug and a carrier. Sustained-release is achieved by a mechanism in which the pharmaceutical preparation adheres to the nasal mucosa, absorbs the mucus and gradually swells while adhering to the mucosa, and gradually the drug is released from the swollen portion. The composition comprises a mucosa-adhesive polymeric matrix comprising from about 50 % to about 95 % by weight of a cellulose ether and about 50 % to about 95 % by weight of a polymer of acrylic acid.

EP-A-0,023,359 discloses a sustained-release, powdery pharmaceutical composition for application to the mucosa of the nasal cavity, comprising a drug and a carrier in which at least 90 % of the composition consists of particles having an effective particle diameter of 20 to 250  $\mu\text{m}$ . The composition comprises a lower alkyl ether of cellulose having a viscosity of 5 to 5000 mPa.s and a drug.

Chitin is widely distributed in nature. It is found in tissue support of crustaceans and insects and chitosan is the deacetylation product thereof. Chitin and chitosan have previously been used in pharmaceutical sustained-release preparations. EP-A-187,703 and US-A-4,814,176 disclose a sustained-release preparation in which a combination of chitin and/or chitosan and an anionic polymer is utilised as a sustained-releasing agent.

It is an object of the present invention to provide a sustained-release powdery pharmaceutical composition with improved adhesion characteristics which provides a high availability of the active ingredient and which solves the problem of "roll-back" associated with nasal sprays.

### Summary of the Invention

According to one aspect of the present invention, there is provided a pharmaceutical composition in the form of a powder for application to the mucosa of the nasal cavity and which comprises a drug and a pharmaceutically-acceptable carrier, the carrier comprising

- a) from about 90 % to about 10 % by weight thereof of a non-ionic cellulose ether derivative and
- c) from about 10 % to about 90 % by weight thereof of a chitin-derived polymer,

and wherein the total amount of cellulose ether derivative and chitin-derived polymer comprises at least about 50 % by weight of the composition.

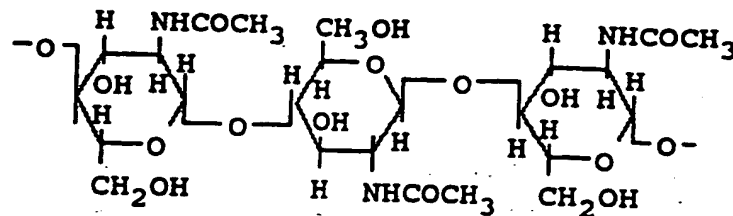
### Detailed Description of the Invention

In accordance with the present invention a powdery pharmaceutical composition is formed comprising a drug and a carrier. The carrier comprises a non-ionic cellulose ether derivative and a chitin-derived polymer.

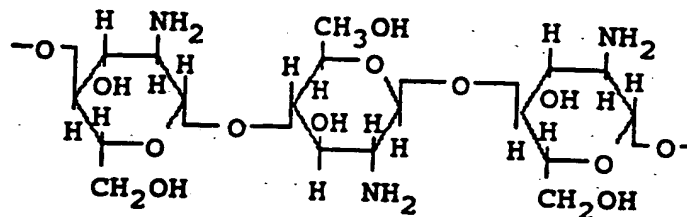
The cellulose ether derivative is present in an amount of about 90 % to about 10 %, preferably from about 85 % to about 45 %, by weight of the carrier. Suitable cellulose ether derivatives include methyl cellulose, thyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose,

hydroxymethyl cellulose, hydroxyethyl cellulose and sodium carboxymethyl cellulose, and mixtures thereof. Preferred cellulose ether derivatives include hydroxy C<sub>1</sub> to C<sub>4</sub> alkyl ether celluloses which have an ether substitution degree of from about 0.1 to 6.0, more preferably from about 0.4 to 0.6, highly preferred being hydroxypropylmethyl cellulose (HPMC). HPMC is well known in the pharmaceutical and food industries as a thickener and suspending agent. It has substantially no odour or irritation associated with it and is therefore preferred for application to the nasal mucosa which is particularly sensitive to odour and irritation. Furthermore, HPMC easily absorbs mucous from the nasal mucosa, thereby giving the pharmaceutical composition effective adhesiveness and flowability on the nasal mucosa. Whilst a variety of grades of the cellulose ether derivative powders may be used it is preferable that a grade of powder should be used which has a viscosity of from about 1 to about 50,000 mPa.s, preferably from about 5 to about 5000 mPa.s (measured at 37°C  $\pm$  0.2°C for a 2 % aqueous solution of the cellulose ether derivative), in order that the pharmaceutical composition of the present invention forms a viscous, flowable liquid on application to the nasal mucosa.

The chitin-derived polymer in the carrier is present in an amount from 10 % to 90 %, preferably from 15 % to 55 %, by weight of the carrier. Suitable chitin-derived polymers include chitin, chitosan and salts, and mixtures thereof. Chitin is derived from naturally occurring substances such as in tissues of crustaceans and insects and chitosan is the deacetylation product thereof. The formula of chitin is (1->4)-2-acetamide-2-deoxy- $\beta$ -D-glucan having the following structure:



Chitosan has the formula (1->4)-2- amino-2-deoxy-β-D-glucan, and has the following structure:



According to the present invention, the preferred chitin-derived polymer is chitosan hydrochloride salt.

Drugs suitable for use in the compositions herein can be selected appropriately according to the disease to which the composition is to be applied. In the present invention the drug is preferably an agent for treating or preventing a nasal disease, preferably a vasoconstrictor or other nasal decongestant. Furthermore the drug should not react with either the cellulose ether derivative or the chitin-derived polymer. Suitable drugs may be in solid or liquid form, preferably solid form.

Examples of such drugs include antipyretic and analgesic agents, antiphlogistics, antiarrhythmics, hypotensors, vasodilators, anticholinergics, antiarteriosclerotics, agents for circulatory systems, antitussives, expectorants, ulcer preventives, enzyme preparations, anti-malignants,

chemotherapeutic agents, antihistamine agents, enzym preparations, local anaesthetic agents, and mouth disinfection agents, steroidal anti-inflammatory agents, non-steroidal anti-inflammatory agent, anti-allergic agents, vasoconstrictors, and mixtures thereof.

In compositions to be used for treating or preventing nasal diseases, drugs effective for treatment or prevention of nasal diseases, such as anti-inflammatory agents, antihistamine agents, anticholinergics, anti-allergic agents or vasoconstrictors, are preferred. A highly preferred drug for inclusion in the composition of the present invention is a vasoconstrictor.

Suitable vasoconstrictors for use herein include phenylephrine hydrochloride, ephedrine hydrochloride, tetrahydrozoline hydrochloride, naphthazoline nitrate, oxymetazoline hydrochloride, xylometazoline hydrochloride and tramazoline hydrochloride, preferably oxymetazoline hydrochloride.

In the pharmaceutical composition of the present invention, it is preferred that at least about 85 % by weight of the entire particles should have particle size in the range from 5 to 250  $\mu\text{m}$ , preferably from 10 to 120  $\mu\text{m}$ . This particular range is chosen such that a higher proportion of powder composition adheres to the nasal mucosa when applied to the nasal cavity.

The desired particulate form and particle size can be achieved by spray drying a solution of the pharmaceutical composition ingredients. Of all the industrial dryer types available, spray drying is unique in being able to produce powders of specific particle size and moisture content irrespective of dryer capacity and product heat sensitivity. Spray drying also ensures



uniform distribution of the active agent and the carrier. Spray drying consists of four process stages: 1) atomization of feed into a spray, 2) spray-air contact, 3) drying of spray and 4) separation of dry product from the air. Each stage is carried out according to dryer design and operation, and together with the physical and chemical properties of the feed determines the characteristics of the dried product. Spray drying techniques are well known in the art and can be applied in preparing the composition of the invention in known manner.

The present invention is illustrated by the following examples.

#### Example 1

A powdery pharmaceutical composition of the invention is prepared as follows:

A stoichiometric quantity of chitosan is mixed with purified water and the pH is adjusted to about 4.5 with 37 % hydrochloric acid. The mixture is stirred for about 2 hours until dissolved. The viscosity of the mixture is then adjusted to 550 cps by the addition of water. Stoichiometric quantities of oxymetazoline hydrochloride and hydroxypropylmethyl cellulose are added with stirring until dissolution is complete. The final solution is filtered by passing it through a centre sieve with a 100  $\mu$ m filter and the resulting mixture is spray dried at a temperature of 105°C and a minimum pump pressure of 200 bar. In order to achieve the required particle size the powder is passed through a 70 mesh sieve. The final composition of the dry, powdery pharmaceutical composition is as follows:

11 % water

43.5 % chitosan hydrochloride salt  
43.5 % hydroxypropylmethyl cellulose  
2.4% oxymetazoline hydrochloride.

Example 2

A second pharmaceutical composition is prepared using the same method as described in Example 1 having the final dry composition:

11 % water  
17.5 % chitosan hydrochloride salt  
69.5 % hydroxypropylmethyl cellulose  
2.4 % oxymetazoline hydrochloride.

The powdery pharmaceutical compositions of the above examples demonstrate improved adhesion characteristics and provide a high availability of active ingredient.

**WHAT IS CLAIMED IS:**

1. A pharmaceutical composition in the form of a powder for application to the mucosa of the nasal cavity and which comprises a drug and a pharmaceutically-acceptable carrier, the carrier comprising

a) from about 90 % to about 10 % by weight thereof of a non-ionic cellulose ether derivative and

c) from about 10 % to about 90 % by weight thereof of a chitin-derived polymer,

and wherein the total amount of cellulose ether derivative and chitin-derived polymer comprises at least about 50 % by weight of the composition.

2. A pharmaceutical composition according to claim 1 wherein the cellulose ether derivative is selected from methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and mixtures thereof.

3. A pharmaceutical composition according to claim 1 wherein said cellulose ether derivative is a hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl ether cellulose, preferably hydroxypropylmethyl cellulose.

A pharmaceutical composition according to claim 1 wherein said cellulose ether derivative has viscosity, determined at 37°C  $\pm$  0.2°C for a

- 2 % aqueous solution, of from about 1 to about 50,000 mPa.s., preferably from about 5 to about 5000 mPa.s.
5. A pharmaceutical composition according to claim 1 having a particle size distribution such that at least about 85 % by weight thereof has a particle size in the range from 5 to 250  $\mu\text{m}$ , preferably from 10 to 120  $\mu\text{m}$ .
6. A pharmaceutical composition according to claim 1 wherein the chitin-derived polymer is selected from chitin, chitosan and mixtures thereof.
7. A pharmaceutical composition according to any of claims 1 to 6, wherein the drug is at least one member selected from antipyretic and analgesic agents, antiphlogistics, antiarrhythmics, hypotensors, vasodilators, anticholinergics, antiarteriosclerotics, agents for circulatory systems, antitussives, expectorants, ulcer preventives, enzyme preparations, anti-malignants, chemotherapeutic agents, antihistamine agents, local anesthetic agents, and mouth disinfection agents, steroidal anti-inflammatory agents, nonsteroidal anti-inflammatory agent, anti-allergic agents, vasoconstrictors, and mixtures thereof.
8. A pharmaceutical composition according to any of claims 1 to 7 wherein the drug is an agent for treating or preventing a nasal disease.
9. A pharmaceutical composition according to any of claims 1 to 8, wherein said drug is a vasoconstrictor.

10. A pharmaceutical composition according to claim 9 wherein the vasoconstrictor is selected from oxymetazoline hydrochloride, xylometazoline hydrochloride, phenylephrine hydrochloride, ephedrine hydrochloride, tetrahydrozoline hydrochloride, naphthazoline nitrate, tramazoline hydrochloride.
11. A pharmaceutical composition according to claim 10 wherein the vasoconstrictor is oxymetazoline.
12. A pharmaceutical composition according to any of claims 1 to 11 wherein the carrier comprises
- a) from about 85 % to about 45 % by weight thereof of the non-ionic cellulose ether derivative, and
  - b) from about 15 % to about 55 % by weight thereof of the chitin-derived polymer.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/04037

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 47/00, 31/415, 31/135

US CL :514/777, 781, 392, 401, 653

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts 104(2):10656y, 1983	1-6 and 10-11
Y	WPI Abstract of JP 62236862, 007334349, WPI Acc. No. 87-331356/47, 1987	1-6 and 10-11
Y	Chemical Abstracts 98(10): 78047p, 1982	1-6 and 10-11
Y	Chemical Abstracts 96(6): 40912n, 1981	1-6 and 10-11

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

Special categories of cited documents:	
*A* document defining the general state of the art which is not considered to be part of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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*O* document referring to an oral disclosure, use, exhibition or other means	*Z* document member of the same patent family
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Date of the actual completion of the international search

14 JULY 1993

Date of mailing of the international search report

16 AUG 1993

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/04037

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<u>The Merck Index</u> (11 <sup>th</sup> Ed.), Budavari et al. (Editors), Merck and Co., Inc., Rahway, NJ, 1989, pp. 565-566, 1008, 1102, 1157-1158, 1453, 1506 and 1591.	10-11
Y	US,A 4,917,899 (Geoghegan et al.)-17 April 1990. See columns 3 and 4 particularly.	1-6 and 10-11
A,P	US,A, 5,122,598, (della Valle et al.) 16 June 1992. See columns 2 and 6 particularly.	1-6 and 10-11
Y	US,A, 4,713,249 (Schröder) 15 December 1987. See columns 2 and 3 particularly.	1-6 and 10-11
Y	US,A, 4,294,829 (Suzuki et al.) 13 October 1981. See abstract and column 4 particularly.	1-6 and 10-11
Y	US,A, 4,603,131, (Bernstein et al) 29 July 1986. See abstract and column 4 particularly	1-6 and 10-11
Y	US,A 4,814,169 (Mitsuhashi et al.) 21 March 1989. See abstract and column 2 particularly.	1-6 and 10-11

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/04037

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 7-9 and 12  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

International application N .

PCT/US93/04037

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

World Patents Index, APS, CAS-chitin or chitosan and etc. and cellulose and various derivatives with nasal powder compositions containing pharmaceuticals especially the vasoconstrictor xymetazoline